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Clinical trial readiness study of distal myopathy and dysphagia in nephropathic cystinosis

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Abstract

Background: Nephropathic cystinosis is a lysosomal storage disorder with late-onset systemic complications, such as myopathy and dysphagia. Currently employed outcome measures lack sensitivity and responsiveness for dysphagia and myopathy, a limitation to clinical trial readiness.

Methods: We evaluated 20 patients with nephropathic cystinosis in two visits over the course of a year to identify outcomes sensitive to detect changes over time. Patients also underwent an expiratory muscle strength training program to assess any effects on aspiration and dysphagia.

Results: There were significant differences in the Timed Up and Go Test (TUG) and Timed 25-Foot Walk (25-FW) between baseline and 1-y follow-up ($P < .05$). Maximum expiratory pressure (MEP) and peak cough flow (PCF) significantly improved following respiratory training ($P < .05$).

Conclusions: Improved respiratory outcomes may enhance patients ability to expel aspirated material from the airway, stave off pulmonary sequelae associated with chronic aspiration, and yield an overall improvement in physical health and well-being.

KEYWORDS

distal myopathy, dysphagia, EMST150, nephropathic Cystinosis, respiratory therapy, video fluoroscopy

1 | INTRODUCTION

Nephropathic cystinosis is a rare autosomal recessive lysosomal storage disorder caused by mutations in the cystinosin gene (*CTNS*), leading to impairment in the lysosomal membrane transport complex.[1-5] Patients often present with early failure to thrive and Fanconi syndrome.[6,7] The free cystine crystal deposition in different tissues including muscle leads to clinical myopathy characterized pathologically by the presence of autophagic, acid phosphatase positive vacuoles in muscle tissues[8,9] and cystine crystals within perimysial collagen fibrils.[5] Oral beta-mercaptoethylamine (cysteamine) facilitates cystine transportation from the lysosome through an alternative lysine transporter[10-12] and lowers cystine levels in the muscle tissue.[13-18] Nevertheless, patients continue to have significant non-renal

Abbreviations: 25-FW, Timed 25-Foot Walk; 9-HPT, 9-Hole Peg Test; ACE, Adult Care Excellence Initiative; ALS, amyotrophic lateral sclerosis; ASHA, American Speech and Hearing Association; DMFS, Distal Myopathy Function Scale; EAT-10, The 10-item Eating Assessment Tool; EMST, Expiratory Muscle Strength Trainer; IQR, interquartile range; MDADI, M. D. Anderson Dysphagia Inventory; MEP, maximum expiratory pressure; PAS, Penetration-Aspiration Scale; PCF, peak cough flow; QOL, quality of life; SLP, speech language lathologist; TUG, Timed Up and Go test; VFSS, video fluoroscopy swallow study.

morbidity and mortality primarily due to muscle weakness,[19-21] swallowing difficulties[22] and aspiration.[23]

There is an increasing awareness that clinical myopathy and dysphagia are common, even in the absence of clinically overt muscle weakness.[16,18,20-22,24-26] Respiratory muscle weakness can be life threatening.[27] In addition, oropharyngeal dysphagia may give rise to aspiration pneumonia and other respiratory complications.[28] It is imperative to develop clinical trial readiness studies to better understand the natural history of the disease, changes in clinically relevant outcome measures, guidance on care standards, and biomarkers that ascertain disease severity or drug response.

Improved swallowing efficiency and elevated tolerance of aspiration can allow a patient to liberalize diet and improve overall quality of life.[29] Expiratory Muscle Strength Trainer (EMST) is an intervention applied in healthy individuals and in patients with the goals of increasing the force generating capacity of the expiratory muscles and improving pulmonary function.[30] EMST is feasible and well tolerated in neurological conditions with prominent dysphagia, improving expiratory force-generating pressures and swallowing kinematics.[31-33] The activation of expiratory musculature is implicated in the force generation of cough.[34] Individuals with chronic dysphagia and associated aspiration, such as in the cystinosis population, benefit from a holistic approach to swallowing management, which includes exercise aimed at improving oral, pharyngeal, and laryngeal physiological function in concert with interventions aimed to protect and clear the airway. Interventions targeted to improve cough, such as expiratory muscle strength training, are an essential component of whole patient focused dysphagia management.

Through collaboration with the members of the Adult Care Excellence (ACE) Initiative[35] and access to the results of qualitative surveys[36-38] from adults patients with nephropathic cystinosis, we determined that swallowing difficulties and muscle weakness were the most pressing concerns affecting quality of life and function. In the first phase of this study, we characterized clinical myopathy, muscle weakness and dysphagia in patients with nephropathic cystinosis and proposed a new disease-specific functional clinical outcome measure to better quantify disease progression in this patient population.[25] In this longitudinal follow-up study, we sought to: (1) further characterize the evolution of the myopathy and dysphagia; (2) evaluate the sensitivity and responsiveness of currently used strength, swallowing, and respiratory outcomes; and (3) evaluate the feasibility of EMST and its impact on swallowing and respiratory outcome measures.

2 | METHODS

The study was approved by the research ethics committee, Partners Institutional Review Board at Massachusetts General Hospital. Informed consent was obtained in accordance with Institutional Review Board procedures.

Patients with confirmed nephropathic cystinosis, based on elevated leukocyte cystine levels, the presence of crystals in the cornea, or genetic mutation testing, had two visits (visit 1 and 2) 1 y apart. Following the second visit, patients underwent a 5-wk exercise regimen using an EMST150 expiratory muscle strength training program. At the completion of the training regimen, patients had an additional visit (visit 3) to identify any effect on aspiration and dysphagia and breathing outcomes.

2.1 | Clinical study

Patients had a neuromuscular examination, including manual muscle testing of proximal and distal upper and lower extremities, video fluoroscopic swallowing evaluation, and pulmonary function testing at each visit. Patients completed patient-reported measures (The M. D. Anderson Dysphagia Inventory[32] [MDADI] and The 10-item Eating Assessment Tool[33] [EAT-10]), and clinical outcome measures (9-Hole Peg Test [9-HPT], Timed 25-Foot Walk [25-FW], Timed Up and Go Test [TUG], and grip myometry).

2.2 | EMST training

EMST150 (Aspire Products; Gainesville, FL, USA) is a handheld device that houses a calibrated spring loaded valve designed to improve activation of the expiratory and submental muscles through resistance training.[39] A 5-wk exercise protocol using this trainer commenced immediately following visit 2. EMST150 was used with the trainer set at 50% of a patients individual maximum expiratory pressure (MEP), representing a moderate load on the expiratory muscles. A flanged rubber mouthpiece was attached to the opening of the trainer to help create a tight lip seal. For those that did not meet the threshold requirements (MEP > 60 cm H_2O), we did not calibrate the device and left it at 30 cm H_2O, the lowest resistance pressure. There was one patient who could not achieve a lip seal around the flanged rubber mouthpiece due to lip and facial weakness. She used a mask that created a seal around the entire mouth and nose and expelled air through the device in this manner. To measure adherence to the treatment protocol, each day of training, patients submitted a video clip of themselves using the EMST150 device along with verbal confirmation of the level they were using.

2.3 | Patient-reported outcomes

The MDADI is a self-administered 20-item questionnaire designed to evaluate the impact of dysphagia on the quality of life (QOL) of patients with head and neck cancer, which we adopted for this study of patients with nephropathic cystinosis. MDADI scores range between 20 and 100, with a higher score representing better function and QOL. The EAT-10 is a self-administered, symptom-specific outcome instrument for dysphagia used in various conditions including neurodegenerative diseases. The EAT-10 scores range between 0and 40, with higher scores representing more severe dysphagia. Normative data suggest that an EAT-10 score of 3 or higher is considered abnormal.

TABLE 1 Clinical and patient-reported outcome measures for visits 1, 2, and 3 and between visit comparisons

		Visit 1		Visit 2		Visit 3		Visits 1–2	Visits 2–3
	Units	Mean (95%CI)	Median (IQR)	Mean (95%CI)	Median (IQR)	Mean (95%CI)	Median (IQR)	*P*-value	*P*-value
MEP	cmH_2O	64.2 (45.9;82.5)	64.4 (29.0;91.5)	63.4 (45.4;81.4)	69.5 (30.3;86.7)	80.9 (60.4;101.5)	94.0 (43.3;106.7)	.781	<.001*
PCF	L/min	249.0 (193.3;304.7)	269.3 (97.3;345.0)	233.2 (184.9;281.5)	253.3 (123.3;293.3)	259.0 (207.5;310.5)	293.4 (146.7;346.7)	.324	.022*
Grip	KgF	23.2 (16.5;29.8)	21.0 (17.2;26.3)	22.2 (17.6;26.7)	21.2 (16.7;27.4)	19.7 (15.4;24.0)	20.9 (17.5;24.8)	.546	.131
9-HPT	Sec	23.3 (20.5;26.2)	21.7 (20.3;25.2)	22.7 (19.7;25.8)	21.0 (18.6;25.5)	22.4 (19.2;25.7)	21.5 (18.1;23.9)	.413	.726
TUG	Sec	7.0 (6.3;7.8)	7.3 (5.8;8.2)	7.9 (7.0;8.8)	7.7 (6.4;8.6)	8.1 (6.9;9.3)	7.6 (6.3;9.2)	.002*	.870
25-FW	Sec	4.9 (4.5;5.4)	5.1 (3.9;5.6)	5.7 (5.2;6.3)	5.3 (4.9;6.4)	5.7 (5.2;6.3)	5.5 (4.8;6.4)	<.001*	.288
MDADI-E	-	24.5 (22.8;26.1)	25.0 (22.5;26.0)	23.3 (20.7;25.8)	24.0 (20.5;26.5)	23.3 (21.2;25.4)	24.0 (22.0;26.0)	.389	.966
MDADI-F	-	19.9 (19.1;20.7)	21.0 (18.0;21.0)	18.5 (16.3;20.8)	20.0 (16.0;21.0)	19.1 (18.1;20.1)	20.0 (18.0;21.0)	.223	.625
MDADI-C	-	77.8 (72.7;82.9)	80.5 (68.5;87.0)	71.3 (62.8;79.8)	77.0 (61.0;88.0)	72.8 (66.1;79.6)	74.0 (60.0;87.0)	.173	.769
MDADI-P	-	33.5 (30.3;36.6)	35.0 (28.0;40.0)	29.7 (24.1;35.3)	32.5 (21.0;40.0)	31.2 (26.9;35.4)	32.0 (25.0;40.0)	.217	.668
EAT-10	-	6.7 (2.7;10.7)	2.5 (0.5;15.0)	6.7 (2.5;10.9)	3.0 (1.0;8.5)	6.3 (2.6;10.0)	3.0 (0.0;13.0)	.594	.149

Abbreviations: MEP, maximum expiratory pressure; PCF, peak cough flow; 9-HPT, 9-Hole Peg Test; PAS, penetration-aspiration scale; TUG, Timed Up and Go test; 25-FW, 25-Foot Walk test; MDADI, The M. D. Anderson Dysphagia Inventory sub scores, emotional (E), functional (F), composite (C), physical (P); EAT-10, The 10-item Eating Assessment Tool.

*$P < .05$.

2.4 | Clinical outcomes

All patients were assessed by board-certified neurologists (R.S., W.S.D., F.E.) who performed neurological evaluations, including manual muscle testing (eye closure, mouth closure, neck flexion/extension, shoulder abduction/external rotation, elbow flexion/extension, wrist flexion/extension, finger extension/abduction, thumb abduction/flexion, deep finger flexion [I-IV], hip flexion/abduction/adduction/extension, knee flexion/extension, ankle dorsiflexion/plantar flexion, toe extension, deep toe flexion) and hand grip strength using a calibrated Jamar Hydraulic Hand Dynamometer. TUG was used to assess each patients mobility, static and dynamic balance, walking ability, and fall risk. 25-FW was administered to assess quantitative mobility and leg function. 9-HPT was used to measure finger dexterity.

A standardized video fluoroscopy swallow study (VFSS) was performed by an American Speech and Hearing Association (ASHA) certified speech language pathologist (SLP) with clinical specialization in swallowing disorders using three food textures of barium contrast (thin, nectar, and pudding), natural sip in the lateral and AP projection. Each patients VFSS was evaluated using the validated Penetration-Aspiration Scale (PAS),[40] an 8-point ordinal scale of airway safety that describes the degree of airway invasion, the participants response, and whether the invasive material is successfully ejected from the airway. A PAS score of 1 indicates that no material entered the airway, and a score of 8 indicates that material entered the airway, passed the level of the vocal cords with no effort to eject. MEP and PCF were used to evaluate respiratory function.

2.5 | Statistical analysis

We used SAS Release: 3.8 (Basic Edition) statistics software for statistical analysis and GraphPad Prism 8 for preparing figures. We tabulated summary statistics for the clinical and patient-reported outcomes. Paired T-tests and Wilcoxon signed-rank test were used to compare changes in scores between visits. A *P*-value of less than .05 was considered significant.

3 | RESULTS

We previously published baseline demographics and characteristics of visit 1 of this study.[25] In summary, a total of 20 patients, 7 male and 13 female, ages 20–64 y (median 29, interquartile range [IQR], [27:39]) participated in the study. In the initial survey, 12 of 20 (60%) of patients reported some degree of difficulty swallowing and 17 of

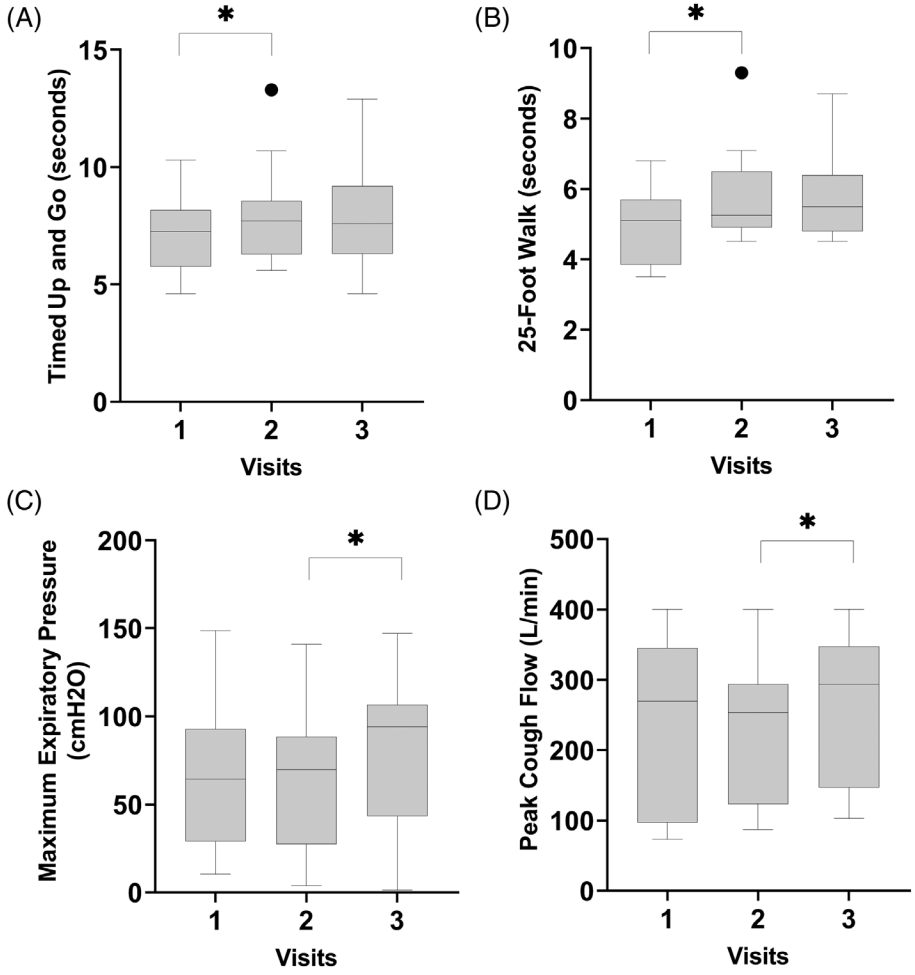

FIGURE 1 Distribution of clinical and respiratory outcomes at visits 1, 2, and 3. Box and whisker plots show the median, upper, and lower quartiles, with outlier values shown as black dots. A, distribution of TUG with significant difference between visits 1 and 2. B, Distribution of 25-FW with significant difference between visits 1 and 2. C, Distribution of MEP with significant difference between visits 2 and3. D, Distribution of peak cough flow with significant difference between visits 2 and 3. * *P*-value < .05 (Wilcoxon signed rank test)

20 (85%) of patients reported some degree of (limb) muscle weakness, primarily in the hands (eg, dropping objects and buttoning). The most severe distal weakness was in the thenar and hypothenar muscles. Neck flexion, shoulder abduction, and hip flexion were weakest among proximal muscles. Additionally, patients had facial and respiratory muscle weakness.

The PAS scores ranged from 1 to 8. Material contacted the vocal cord without clearing the larynx (PAS 5) in one patient, and material entered the trachea without attempt to clear (PAS 8) in two patients.

There were significant differences at visit 1 and 2 between TUG and 25-FW (Table 1, Figure 1). There were no significant changes in EAT-10, MDADI, 9-HPT, grip myometry, or manual muscle strength testing over the course of the observational phase of the study or following the exercise regimen. Two patients had a worsening PAS score from visit 1 to visit 2.

Respiratory outcomes, MEP and PCF, significantly improved following respiratory training program (Table 1, Figure 1). Of seven (7/20) patients who could not generate expiratory pressure greater than 60 cm H20 at the beginning of the 5-wk trial, five (5/7) patients demonstrated improved ability to expel air through resistance by the end of the study.

Videofluoroscopic evaluation at visit 3 was notable for improvement in the three patients with baseline high PAS scores (visit 2, PAS 8; visit 3, PAS 5) and mild worsening in one patient (visit 2, PAS 1; visit 3, PAS 3). There were no associated changes in patient-reported dysphagia outcomes for these patients. One of three patients with better PAS also had modest improvement in MDADI-e (visit 2, 20; visit 3, 24), MDADI-f (visit 2, 12; visit 3, 17), MDADI-p (visit 2, 18; visit 3, 19), MDADI-c (visit 2, 50; visit 3, 60), and EAT10 (visit 2, 23; visit 3, 20) scores.

4 | DISCUSSION

We previously demonstrated that progressive muscle weakness and dysphagia were common in adult patients with nephropathic cystinosis.[18,21,22] In the observational phase of this study, we could detect changes in TUG and 25-FW over time. Most of our cohort had distal upper extremity weakness, but the outcome measures used failed to detect a significant change in upper extremity strength. Similarly, clinical and patient-reported dysphagia outcomes failed to capture significant changes over 1 y. Following our respiratory exercise program, patients improved in their respiratory function, which may have reduced aspiration risk in those with more severe dysphagia.

While most participants endorsed a certain degree of difficulty swallowing, the objective swallow testing identified dysphagia only in three patients, raising the possibility that currently used outcome measures lack sensitivity to capture the severity of dysphagia. In this study, we measured severity of dysphagia using PAS, a scale of airway invasion during swallowing only. The most dysphagic patients are those with aspiration/penetration of contrast into the laryngeal vestibule before, during, or after the pharyngeal swallow response. Expansion of our measurements to include ratings of "post swallow residue in the pharyngeal recesses" and "time of pharyngeal swallow onset and laryngeal closure" may expand the number of patients we classify as having severe dysphagia. Similar to other primarily neuromuscular conditions, the exact pathophysiology and dynamics of dysphagia are not well characterized in nephropathic cystinosis.[21,22]

Oropharyngeal dysphagia may give rise to aspiration pneumonia and other respiratory complications. In addition, patients living with chronic dysphagia may struggle with the ability to achieve optimal nutrition and hydration, complications that can promote weakness, fatigue, and hospitalization. Patients with cystinosis require an enormous amount of oral medications to manage their disease and post-transplant complications. Depending on the severity of dysphagia, taking these medications several times per day is not only difficult and stressful but can be dangerous.

Extending from more recent studies in patients with amyotrophic lateral sclerosis (ALS) and other neurodegenerative processes, we investigated the role of targeted exercise in ameliorating symptoms in the cystinosis population. The impact of EMST in this cohort is similar to that reported in patients with ALS, Parkinsons disease, and multiple sclerosis.[32,41-44] In the interventional phase of this study, patients with more severe dysphagia showed modest improvements in the PAS score. This may suggest a benefit in more severely affected patients or indicate that the conventional scoring lacks the sensitivity to capture dysphagia in more mildly affected patients.[40] A multitude of factors may explain the modest decline in PAS of one the patients, including lack of efficacy (only modest improvement in respiratory metrics), overall disease progression, fatigue at the time of testing, or the lack of sensitivity or variability of testing. A more detailed kinematic, temporal, and functional examination of swallowing could help further characterize the underlying pathophysiology and serve as a more sensitive, responsive, and predictive outcome measure.[45] The exercise was well-tolerated without any major complications. Previous studies in a variety of neurological conditions also showed significant improvement in MEP post-EMST.[31,32,46,47] Despite improvement in some patients, other studies also found no significant changes in swallowing safety metrics such as PAS, likely pointing to the variable responsiveness and sensitivity of these scoring systems.

Our data must be interpreted in the context of the study design. Although there were statistically significant differences noted between some time points for clinical and respiratory outcomes, there was considerable overlap of the values likely due to the small sample size. Furthermore, both TUG and 25-FW are measures of ambulation, functions that are not typically affected in patients with cystinosis. The lack of association with other measures, such as respiratory and upper extremity outcomes, hampers concept validity of these measures. Additionally, relatively small changes using a measurement with a low signal-to-noise ratio necessitates a larger sample size, a major obstacle in rare diseases.[48]

In nephropathic cystinosis, progressive muscle weakness has emerged as a potential limitation of otherwise effective therapy, such as oral cysteamine treatment. Currently used clinical outcomes and biomarkers lack granularity to capture meaningful changes in disease severity in patients affected by dysphagia and distal myopathy.[49] A

more extensive longitudinal study would help evaluate the responsiveness of outcome measures used in this study and enable future clinical trial readiness.

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ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

CONFLICTS OF INTEREST

None of the authors have any conflict of interest to disclose.

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